REMARKS

Claims 1, 4-9, and 11-15 are pending. Claims 1, 5, 6, 9, and 11 have been amended. Claims 5 and 11 have been amended to correct inadvertent typographical errors, and claim 6 has been amended to correct a minor grammatical error. Claims 1 and 9 have been amended to recite "in suspension." Support for this amendment may be found throughout the application as filed, including, for example, at page 1, lines 15-17, and at page 4, lines 8-9. Thus, the amendments to the claims do not introduce any new matter.

1. Summary of Patent Office Interview

The Applicants gratefully acknowledge the courtesy shown by the Examiner during the interview conducted on June 30, 2011, in which the prior art rejections were discussed.

2. Claim rejections under 35 USC §112, Second Paragraph

(A) The Patent Office has maintained its rejection of claims 1, 4-9, and 11-15 under 35 USC §112, second paragraph, as being indefinite, based on the assertion that the functional language is confusing. Specifically, the Patent Office asserts that the functional limitations "wherein no more than 5% of the animal cells in the culture form aggregates of at least 5 cells during the continuous perfusion culturing" and "resulting in an outflow of liquid having a lower animal cell density than the cell culture" are confusing because it is not clear whether these effects are an inherent result of some process steps or whether some additional step is required to achieve this result. The Patent Office has also specifically noted that claims 8 and 9 suffer from the same alleged deficiencies. Applicants respectfully traverse these assertions.

As a preliminary matter, applicants note that a portion of the allegedly confusing language of claim 1 quoted by the Patent Office – "resulting in an outflow of liquid having a lower animal cell density than the cell culture" – was amended in Applicants' previous response to further clarify the nature of the claimed invention.

In setting forth its rejection the Patent Office has stated that the "Applicant has not clearly admitted on the record that all methods that include… inherently yield the recited outcome" and that "Applicant has also not clearly stated that no additional steps

or conditions are necessary…" However, the Patent Office has not set forth *any* legal basis for requiring any such admission or statement on the part of the Applicants.

"The legal standard for definiteness [under the second paragraph of 35 U.S.C. § 112] is whether a claim reasonably apprises those of skill in the art of its scope." *Ex parte Leng*, 2010 Pat. App. LEXIS 15076 at *2 (Pat. App. 2010), *citing In re Warmerdam*, 33 F.3d 1354, 1361 (Fed. Cir. 1994). A claim is indefinite only where its scope "is not clear enough that a person of ordinary skill in the art could determine whether a particular [product or method] infringes or not." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC,* 349 F. 3d 1373, 1384 (Fed. Cir. 2003). Furthermore, "[t]he definiteness of the language employed in a claim must be analyzed not in a vacuum, but in light of the teachings of the particular application." *Ex parte Leng*, 2010 Pat. Appl. LEXIS at *2, *citing In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971).

Moreover, functional limitations may be used in claims, with no additional explanation or admission needed. "There is nothing inherently wrong with defining some part of an invention in functional terms or based upon specified properties. The identification of a component based on its characteristics does not, in and of itself, render a claim improper." *Id.* at *3. "As explained in *In re Swinehart*, 58 C.C.P.A. 1027, 439 F.2d 210, 213 (CCPA 1971), a functional limitation covers all embodiments performing the recited function." *Geneva Pharms.*, 349 F.3d at 1384.

As shown in paragraphs 10-12 of the Zijlstra Declaration, claims 1, 4-9, and 11-15 meet the legal standard for definiteness. In particular, one of skill in the art, particularly in light of the specification, would readily be able to ascertain the scope of the claims – and whether a particular method would infringe the claims as pending.

It is noteworthy that the specification teaches why aggregation of suspended cells is problematic and the level where it is particularly problematic (*see, e.g.* page 1, lines 19-23) and the manner in which the invention reduces such cell aggregation (*see, e.g.*, page 3, line 35 – page 4, line 9). Further, the specification defines aggregating cells (*see, e.g.* page 4, lines 10-15), and teaches how such cell aggregation may be measured (*see, e.g.* page 4, line 24). Additionally, the specification provides adequate context and meaning to the phrase "resulting in an outflow of cell culture liquid through the pores of the filter module having a lower animal cell density per ml than the cell culture prior to circulating through the filter module."

As such, the metes and bounds of the functional limitations of "wherein no more than 5% … during the continuous perfusion culturing" and "resulting in an outflow…than

the cell culture prior to circulating through the filter module" would be readily understood by one of skill in the art, and do not render the pending claims indefinite. Likewise, as shown in paragraph 15 of the Zijlstra Declaration, one of skill in the art would readily understand the scope of claims 8 and 9. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

(B) The Patent Office has maintained its rejection of claims 1, 4-9, and 11-15 under 35 USC §112, second paragraph, as being indefinite, based on the assertion that it is not clear whether the phrase "lower animal cell density" refers to the number of cells per volume of medium or to cells that are lower in density than other cells. Applicants respectfully contend that the Office has failed meet its burden in examining the claim as it relates to this term. "In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises *one of ordinary skill in the art* of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph..." MPEP 2173.02 (emphasis added). Additionally, "[t]he definiteness of the language employed in a claim must be analyzed not in a vacuum, but in light of the teachings of the particular application." *Ex parte Leng*, 2010 Pat. Appl. LEXIS at *2.

The phrase "lower animal cell density" cannot be viewed independently from the remainder of the claim, but rather must be reviewed in context. Claim 1 recites "a lower animal cell density per ml than the cell culture prior to circulating through the filter module" in relation to "lower animal cell density." Moreover, the specification teaches that the claimed methods relate to culturing cells by perfusion culturing (see, *e.g.*, page 1 lines 6-7), and notes that perfusion culturing of cells has its conventional meaning in the art (see, *e.g.*, page 1, line 35 to page 2, line 2). One of skill in the art would have familiarity with perfusion culturing and, as shown in paragraphs 10 and 13 of the Zijlstra Declaration, would readily be able to understand the scope and meaning of "lower animal cell density" as used in claim 1, in view of the specification. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

(C) The Patent Office has rejected claim 4 under 35 USC §112, second paragraph, as being indefinite, based on the assertion that the nature of the compensation in the phrase "to compensate for the biomass removal" is unclear. Again, Applicants note that "[t]he legal standard for definiteness [under the second paragraph of 35 U.S.C. § 112] is whether a claim reasonably apprises those of skill in the art of its scope," and "[t]he definiteness of the language employed in a claim must be analyzed

not in a vacuum, but in light of the teachings of the particular application." *Ex parte Leng*, 2010 Pat. App. LEXIS 15076 at *2. The specification discusses the process of removing biomass and adding cell culture to compensate for the biomass removal (see page 5, line14 through page 6, line 3). As shown in paragraphs 10 and 14 of the Zijlstra Declaration, one of skill in the art, in view of these teachings in the specification, and in view of his/her knowledge of perfusion cell culturing, would readily understand the metes and bounds of claim 4, including the phrase "to compensate for the biomass removal." Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

3. Claim rejections under 35 USC §103

The Patent Office has maintained its rejection of claims 1, 4-9 and 11-15 under 35 USC 103(a) as being obvious over Kyung et al. in view of Shevitz and Furey. Specifically, the Patent Office asserts that Kyung teaches continuous perfusion of mammalian cells in a bioreactor until the cells reach an approximate density of 100×10^6 cells/ml, and also teaches optimizing the calcium concentration of the medium in order to reduce cell aggregation. Shevitz is cited for its teaching of alternating tangential flow, and is asserted to teach that its bioreactor eliminates large cell aggregates in cell culture. Furey is cited for its teaching of culturing cells that produce biological products in the Shevitz bioreactor. The Patent Office further asserts that the pending claims would be obvious to those of skill in the art by combining the teachings of Kyung, Shevitz, and Furey, and that "[t]he skilled artisan would have had a further reasonable expectation of confining cell aggregates to less than 5% of the total cell culture and few than 5 cells per aggregate because Kyung teaches that aggregate formation may be controlled by optimizing the contents of the culture medium and Shevitz's ATF bioreactor is specifically designed to eliminate cell aggregates and to inhibit their formation." Applicants traverse this rejection.

While "[t]he prior art reference (or references when combined) need not teach or suggest all the claim limitations... [the Office Action] must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art." MPEP 2141. Applicants respectfully contend that the Office Action has failed to meet its burden in explaining why the gap between the prior art and the invention as claimed in the amended claims would be obvious to one of skill in the art.

In particular, Applicants contend that the Office Action has failed to adequately support its assertion that one of skill in the art would find the following limitations of the presently claimed invention obvious, in particular when taken in combination:

(1) "wherein no more than 5% of the animal cells in the culture form aggregates in suspension of at least 5 cells" – each of the references is silent on this limitation, and in fact is silent on *any* particular level of aggregation, and/or how to minimize aggregation to this level. At best, the references merely note that aggregation is disfavored.

(2) "continuous perfusion culturing is continued until animal cells are present in the cell culture at a density of at least 80 x 10^6 viable animal cells/ml" – the high density of viable cells is also not taught by any of the cited references.

As shown in paragraph 16 of the Zijlstra Declaration, these elements represent a non-obvious advance over the prior art.

Moreover, the Office Action's reliance on Shevitz, even in combination with the remaining references, is misplaced. As previously noted, Applicants disagree with the Office's position that Shevitz teaches cell aggregation, versus aggregation of non-cellular particles. Nevertheless, even assuming, *arguendo*, that the Office's interpretation of Shevitz is correct, it is abundantly clear that Shevitz is concerned only with a reduction in particle aggregation build up *at the filter* of the bioreactor, as noted in paragraph 17 of the Zijlstra Declaration. As shown and discussed in paragraphs 18-21 of the Zijlstra Declaration, every reference in Shevitz to aggregation is in conjunction with build-up (and clogging) at the filter (emphasis added):

- Column 1, lines 54-57: "However, many of these **filters** have short operating lives, and when used to filter cell culture suspension or other biological fluids they **tend to clog with** dead cells, cell debris, **aggregates** or other constituents of the fluid."
- Column 2, lines 54-56: "The resulting build up of dead cells and **aggregates on** screens or **filters**, **resulting in clogging** and failure of the perfusion device."
- Column 3, lines 37-41: "Recirculation in one direction through the hollow fiber cartridge typically results in **clogging of the hollow fiber lumen by aggregates lodging at lumen inlet. Such aggregates may grow in size** and as more hollow fibers are blocked, filtration capacity declines."
- Column 14, line 64 through column 15, line 7: "The dynamics of the inventive system can extend the operating life of a perfusion run since pulsating flow between vessel 2 and chamber 30 greatly **inhibit the attachment of aggregates to the hollow fiber lumen or to the filter membran**e. For example, as culture medium flows from vessel 2 to pump 34, **aggregates**

> that are larger than the inside diameter of the hollow fibers **will be retained by the hollow fiber array; i.e., the hollow fibers will act as a filter**, however, by repeated and rapid reversal of flow direction, **the deposited aggregates are quickly removed and swept back to the vessel**."

In contrast, however, and as shown in paragraph 22 of Zijlstra Declaration, the presently claimed invention is directed to a reduction in aggregation of cells *in suspension*. And even more particularly, the presently claimed invention is directed to reducing cell aggregation in suspension to where no more than 5% of the cells in culture form aggregates in suspension of at least 5 cells – in a high density culture of viable cells of at least $80x10^6$ viable cells/ml. This, as noted in paragraph 22 of the Zijlstra Declaration, is counterintuitive, and surprising and unexpected to one of skill in the art, as one of skill in the art would expect an increase in aggregation in suspension as the cell density increases, and a significant level of aggregation at a high cell density, which is precisely what Kyung shows.

The Office Action asserts that "[t]he skilled artisan would have been motivated to substitute Shevitz's ATF bioreactor for Kyung's because Shevitz's bioreactor prevents the formation of cell aggregates, which Kyung recognized as being undesirable in suspension culture of mammalian cells" (Office Action, page 7). To the contrary, Shevitz is focused on an entirely different problem than aggregation in suspension, and as shown in paragraph 23 of the Zijlstra Declaration, is silent on the reduction of viable cell aggregation in suspension. Rather, Shevitz seeks to minimize clogging at the filter by aggregates, rather than reducing aggregates *before* they form in suspension. In fact, as shown in paragraph 23 of the Zijlstra Declaration, Shevitz implicitly accepts aggregation of cells in suspension, in simply seeking to minimize the problems of other types of aggregation cause at the filter surface or inlet. To that end, Shevitz in fact *teaches away* from the present invention, which seeks to minimize aggregation of cells in suspension. Thus, the teachings of Shevitz relied upon by the Office Action in asserting the obviousness of the present invention are inapposite.

Kyung and Furey offer nothing more, alone or in combination with Shevitz, that would render the claimed invention obvious to one of skill in the art. Kyung recognizes the problem of aggregation in cell culture, and teaches that Ca^{2+} levels in the culture medium can affect the formation of aggregates, but offers nothing more. In fact, as shown in paragraph 24 of the Zijlstra Declaration, Kyung shows the difficulties faced by one of skill in the art in reducing aggregation of cells in suspension. Kyung teaches the

use of a cell culture medium comprising 100 um Ca^{2+}, presumably a level designed to minimize aggregation based on the statement that "293 cells form aggregates at high Ca^{2+} concentration," but notes that "over a prolonged cultivation period, some large aggregates did form." Furthermore, again as shown in paragraph 24 of the Zijlstra Declaration, Kyung found a significant level of cell aggregation in suspension over a prolonged period of culturing, and at a high cell density (which is still lower than the viable cell density of the presently pending claims). Figure 4 shows, as indicated in paragraph 24 of the Zijlstra Declaration, confocal micrographs of such aggregates at two different time periods (120/125 hour culture sample and 350 hour culture sample), which show quite large clumps of cells that clearly contain many more than 5 cells, and which contain many dead cells. Thus while Kyung recognizes the problem of cell aggregation in suspension, it leads one of skill in the art to conclude that such cell aggregation will remain a problem even when efforts are made to mitigate it, as shown in paragraph 25 of the Zijlstra Declaration. Certainly nothing in Kyung suggests being able to achieve a reduction in aggregation of cells in suspension as the methods of the present invention achieve. Moreover, in view of the absence of any teaching in the other cited references of minimizing cell aggregation in suspension, the combined references as a whole fail to lead one of skill in the art to the presently claimed invention.

Furthermore, as shown in paragraphs 26-27 of the Zijlstra Declaration, none of the claimed references, alone or in combination, render obvious a method of limiting cell aggregation in suspension in cell culture where animal cells are present in the cell culture at a density of at least 80 x 10^6 *viable* animal cells/ml. Contrary to the assertion of the Office Action (see page 7, lines 5-6), Furey does not "recognize perfusion culture, and specifically the ATF bioreactor, is useful for yielding cultures with high viability and high cell concentration." As noted in paragraph 26 of the Zijlstra Declaration, Furey notes that the ATF System can be used for larger scale culturing, and can operate for many days, but it makes no reference to cell viability or concentration, in particular at least 80 x 10^6 viable animal cells/ml, and even more particularly, where no more than 5% of the animal cells in the culture form aggregates in suspension of at least 5 cells. As noted in paragraph 26 of the Zijlstra Declaration, Shevitz is also silent in this regard, other than to note that dead cells – *i.e.* unviable cells – cause problems with clogging at the filter (see, *e.g.* column 2, lines 54-56). As noted in paragraph 27 of the Zijlstra Declaration, Kyung teaches particular cell densities, but not to the level recited in the present claims, and, more significantly, with a much higher level of cell aggregation in

suspension than the present invention achieves. Thus one of skill in the art would not be led to believe that Kyung's methods could be modified to achieve a *greater* density of viable cells, with *less* aggregation of suspended cells, as the present invention achieves. In fact, as noted in paragraph 27 of the Zijlstra Declaration, Kyung would lead one of skill in the art away from the present invention, in teaching that greater cell densities lead to a significantly lowered level of cell viability and larger aggregates.

Based on the above, and as noted in paragraph 28 of the Zijlstra Declaration, one of skill in the art would not find the claimed invention obvious over the cited references.

Furthermore, Applicants note that unexpected results may overcome a *prima facie* case of obviousness, and that rebuttal arguments on this basis must by considered by the Office. MPEP 2145. While Applicants maintain that a *prima facie* case of obviousness has not been established by the Office Action, they nevertheless contend that even if one had been established, it would be overcome by the unexpected results associated with the present invention.

Those of skill in the art, as shown in paragraph 29 of the Zijlstra Declaration, would have found it surprising that the claimed methods could confine suspended cell aggregates to less than 5% of the total cell culture and fewer than 5 cells per aggregate. As noted in the specification, this a surprising finding because low shear conditions, such as in continuous perfusion cell culturing typically do not lead to disaggregation of cells. As noted in the Zijlstra Declaration at paragraph 29, cell aggregation during perfusion cell culturing is disadvantageous, because process control is more difficult, due to, for example, the heterogeneity in metabolic profiles of cells within the cell aggregates. As noted in the Zijlstra Declaration at paragraph 29, this is especially troublesome if cells form aggregates of 5 cells or more and when the aggregates comprise in total 5% or more of the total amount of cells.

Based on all of the above, it is clear that the claimed methods are not obvious over the combination of cited art. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

If the Examiner has any concerns regarding this Response, he is encouraged to contact the undersigned attorney as indicated below at 312-913-2106.

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